LETTERS TO THE EDITOR

Scope

Heart welcomes letters commenting on papers published in the journal in the previous six months. Topics not related to papers published earlier in the journal may be introduced as a letter: letters reporting original data may be sent for peer review.

Presentation

Letters should be:

- not more than 600 words and six references in length
- typed in double spacing (fax copies and paper copy only)
- signed by all authors

They may contain short tables or a small figure. **Please send a copy of your letter on disk.** Full instructions to authors appear in the July 1999 issue of *Heart* (page 116).

Transcatheter closure of atrial septal defects

EDITOR,—Rigby's editorial on transcatheter closure of atrial septal defects is a generally well written review,[1] but several misconceptions pertaining to buttoned device are apparent.

Device delivery sheath—Rigby states that the buttoned device is delivered through a 6–8 F catheter. In each of the publications on this device,[2–7] it is clearly stated that the device is delivered via an 8–9 F sheath.

Device retrieval—Rigby stated that the retrieval is difficult. The device can easily be retrieved transvenously[7] with the help of the loading wire. To prevent inadvertent disconnection of the loading wire with the occluder, we use an additional snare. Even after release from the loading wire, the device can be retrieved by use of a simple snare. However, the device is damaged during the retrieval and cannot be reused.

Embolisation rate—The embolisation rate quoted by Rigby for the buttoned device was 10%, which is very high and we believe is unsupported by the data. In the first 180 implantations in the international trial,[7] there were 13 unbuttonings and one whole device embolisation giving a 7.8% device dislodgement rate for the entire cohort. That trial also showed that there was a decrease in the unbuttoning rate with successive generations of the device: 1st generation, 11.1%; 2nd generation, 9.4%; 3rd generation, 3.1%. In the 4th generation device with two spring buttons, the unbuttoning rate has further decreased ($p < 0.001$) to less than 1.0%.[8 9]

Occlusion of large defects—Rigby's statement that the buttoned device, along with other devices, has only been used for defects up to 20 mm, except for his preferred Amplatzer device, which has been used for sizes up to 34 mm, is incorrect. The buttoned device has been used in hundreds of large defects, often more than 30 mm in diameter; the results were as effective as in small defects, provided that the septal rims are adequate.[10]

Residual shunt rate—It was stated that the buttoned device has the highest residual shunt rate compared with all previous devices. A careful comparison of residual shunts for all devices[11 12] revealed similar residual shunt rates. Furthermore, the effective occlusion rate with non-measurable residual shunt is excellent acutely, and has further improved with follow up.[6 7 13] The Nitinol mesh of the Amplatz device has better acute full occlusion rates, but the buttoned device has achieved good long term results because of better endothelialisation of the polyurethane foam. Elimination of residual shunts is possible with better centring and the use of inverted counteroccluders, with the newer modifications of the buttoned device like the centring and centring on demand buttoned devices.[10]

The reason for these misconceptions is not clear, but is probably related to referring to an abstract[14] from our group while ignoring many full papers in a variety of journals[2–8 13 15–18] including the full paper[13] of the referenced abstract.[14] Or it may be related to relying on personal communications in preference to objective, peer reviewed, published data.[7 9]

Another issue worthy of discussion is wire problems and chronic wire toxicity. Rigby has only superficially touched on the wire problems of the different devices, both acutely and on follow up. Acute problems, including atrial perforation and interference with heart valves, have been shown with all devices. Wire fractures up to 80% have been shown with the Clamshell device[19] and with its successor the CardioSeal device (10% for the first year only). Among all metals used with the different devices, Nitinol has the most acute and chronic complications, despite its very attractive functional characteristics. Unfortunately, chronic nickel toxicity is not simply theoretical, as Rigby mentioned, but rather a well established fact. Hundreds of people have died from lung cancer in the nickel mines, coronary spasm has been shown in experimental animals, and allergic reactions and tissue necrosis are well known. We believe that in 30–50 years time many wires in all devices will be fragmented and some others will have demonstrated some toxicity.

Although the 10 year follow up of the buttoned device showed less than 1% wire related problems, we believe that there is a need for wireless non-toxic devices for heart defect occlusion. We believe that all current disc devices have the same limitations and very similar application and we do not believe that the Amplatz, CardioSeal or the buttoned device can correct more defects than any other. Perhaps a significant factor for the proper device selection is the cost and availability. For countries more price conscious than USA and the UK the fact that the Amplatz device is four times more expensive than the buttoned device can be important. The availability of excellent long term results with one device,[9 13 20] and the absence of long term follow up with the others is another factor. However, we agree with Rigby in his assessment that "none of the devices is perfect, each having its own strengths and weaknesses" and "the modifications of the existing devices and the introduction of new systems will result in current practice changing rapidly in the near future."

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Coronary pressure measurements: catheter induced errors

EDITOR,—Coronary pressure derived fractional flow reserve (FFR), as reviewed by Pijls and Bruyne,[1] provides an excellent and reproducible technique to estimate the severity of a coronary lesion, and is a significant advance over coronary flow reserve. Three points need to be raised.

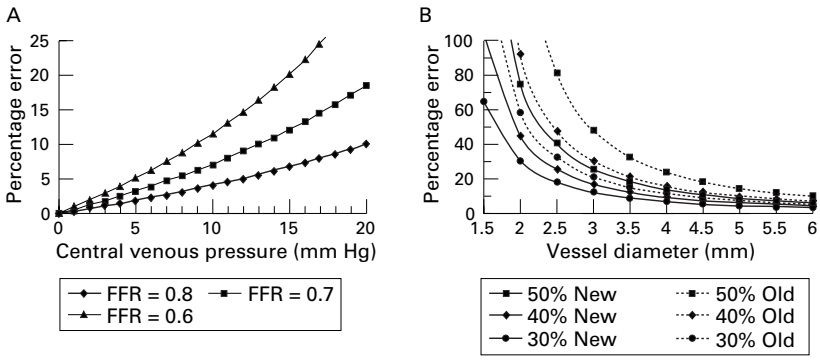

Figure 1 (A) Percentage error for various CVPs. Data are shown for FFRs of 0.6, 0.7, and 0.8. A CVP between 5 and 10 mm Hg can incur a significant error if ignored. (B) Percentage error for various diameter vessels. Data are shown for stenosis of 30%, 40%, and 50%. Data for 0.018" (Old) catheters is shown compared to the newer 0.014" (New) catheters, so that the advance in catheter technology can be appreciated.

First, the arterial pressure measurement should be taken during diastole as most coronary flow is during diastole (not strictly true for the right ventricle). Using mean arterial pressure will induce significant errors.

Second, calculations of FFR without full assessment of the central venous pressure (CVP) may incur significant errors, as the vast majority of patients do not have a CVP of 0. The percentage error incurred when the CVP is not included can be calculated from equation 1.

$$\text{Percentage error in FFR} = \frac{\text{Pcvp.}\ (\text{Pa}+\text{Pd}).100}{\text{Pd.}(\text{Pa}-\text{Pcvp})} \quad (1)$$

Where Pa = arterial pressure; Pd = distal pressure; and Pcvp = central venous pressure.

This is graphically illustrated in fig 1A, which shows that the percentage error incurred is significant.

Finally, even though catheter technology has advanced significantly over the past decade resulting in decreased physical size and increased flexibility, sources of error resulting from the physical size of the catheters should be appreciated if correct interpretations of the readings and derived FFR they produce are to occur. Figure 1B shows the percentage error incurred in vessels of varying diameters with a 30%, 40%, and 50% stenosis. The percentage error can be approximated by equation 2.

$$\text{Percentage error} = (1-(Rv^2.Ps^2\ (Rv^2.Ps.^2-Cd^2/2)^{-2})^2)*100 \quad (2)$$

Where Cd = catheter diameter; Ps = percentage stenosis/100; and Rv = vessel radius.

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1 Pijls NHJ, De Bruyne B. Coronary pressure measurements and fractional flow reserve. *Heart* 1998;**80**:539–42.

This letter was shown to the authors, who reply as follows:

We acknowledge the comments by Dr Poullis and his careful thoughts about coronary pressure measurement. During rest, in the left coronary artery blood flow occurs predominantly during diastole. However, in the presence of maximum coronary vasodilation systolic blood flow also occurs, and in a normal artery this systolic flow constitutes about 25% of total flow. Therefore, as coronary pressure measurements should be performed during maximum coronary vasodilation, the systolic component cannot be neglected. We have demonstrated in our earlier animal studies that it is the mean coronary pressure in the distal coronary artery that determines the FFR by direct comparison to Doppler flow velocimetry in animals and by positron emission tomography in human subjects.[1 2]

We also showed in that study that measuring only diastolic pressure would not make much difference, but the problem in clinical practice is that there is not one diastolic pressure, and therefore mean pressure is more suitable and practical. Again, all validation studies used mean coronary pressure and it is this pressure that has the best correlation with blood flow. For the right coronary artery this issue is even more applicable because here blood flow is often equally distributed between systole and diastole.

The second issue, the implication of central venous pressure, is well regarded but has little practical implications for decision making in the catheterisation laboratory. As nicely illustrated by Dr Poullis's equation, at an FFR of 0.75 (cut off point at diagnostic catheterisation) neglecting central venous pressure results in an error in fractional flow reserve of 2.5% if central venous pressure is as high as 10 mm Hg. Only at very low values of FFR is central venous pressure more important, but decision making in such low values of FFR is trivial. At clinical decision making after a coronary intervention (cut off point 0.9), there is an error of less than 1.5% even in the presence of central venous pressure as high as 10 mm Hg. Therefore, for practical decision making, with respect to the question whether a particular stenosis should be dilated, and whether the result of an intervention is optimal, central venous pressure can be neglected if it is not extremely raised.[3 4]

When fractional collateral blood flow is assessed, it is advisable to include central venous pressure because in that case larger mistakes can be made.[5]

With respect to the possible overestimation of stenosis severity by the presence of the wire, we also considered these theoretical considerations and have examined this in an in vitro study.[6 7] We showed that the influence of the wire on stenosis haemodynamics and gradient is negligible in the range of stenoses where functional assessment is desirable. Only in cases of very severe stenoses will considerable overestimation of the gradient occur, but in that type of stenosis there will be a large gradient and FFR will be well below 0.75. Therefore, in the range of stenoses in which measurement of FFR is desirable, no mistakes are made by the presence of the wire.

In summary, to calculate FFR, mean distal coronary pressure at hyperaemia should be measured; central venous pressure can be neglected as long as it is not very high, unless fractional collateral blood flow is calculated; and in the range of stenoses where physiological measurements are needed, no additional significant gradient is introduced by the presence of the pressure wire.

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Diamorphine and British cardiology: so we are right!

EDITOR,—Diamorphine has been used extensively in cardiology in the UK in the management of acute left ventricular failure, unstable angina, and for relieving pain during a myocardial infarction. Our European and American colleagues however remain firmly committed to the use of morphine for the same clinical situations. To date no studies have revealed any difference in efficacy between morphine and diamorphine.

Ischaemic preconditioning is thought to play an important role in reducing the severity of myocardial damage in acute coronary events.[1] Implementation of ischaemic preconditioning however remains clinically impractical.

The recent discovery that activation of the opioid δ receptor on the myocardium can exert a protective effect to myocardial ischaemia similar in extent to classic ischaemic preconditioning may have important implications.[2] Morphine is known to act predominantly via the opioid μ receptor while diamorphine acts at the δ receptor.[3 4] By implication, diamorphine could offer the benefits of ischaemic preconditioning to patients who receive it compared to those who receive morphine.

Unfortunately adequate numbers and practicalities of patient stratification would make a clinical study difficult, especially for two off patent drugs; however, we may still be right.

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Decrease of plasma fibrinogen after eradication of *Helicobacter pylori* infection in patients with ischaemic heart disease

EDITOR,—Infectious agents such as *Chlamydia pneumoniae* or *Helicobacter pylori* have been linked to ischaemic heart disease (IHD).[1 2] Raised plasma fibrinogen has been claimed as a possible link between *H pylori* infection and IHD[3 4]; however, fibrinogen as an acute phase protein may only reflect systemic inflammation from other underlying diseases (usually not considered in previous publications).

Our aim was to evaluate retrospectively a possible relation between *H pylori* infection, plasma fibrinogen, and IHD. We then planned to test the hypothesis that raised fibrinogen induced by *H pylori* is only important in patients with IHD in the absence of other systemic inflammation parameters.[5] Finally, we attempted to lower plasma fibrinogen in this subgroup of patients by eradicating *H pylori*.

We examined the notes of all patients referred for coronary artery angiography (at least two weeks after myocardial infarction) from August 1994 to August 1995 with suspected or proved IHD for routinely analysed plasma fibrinogen and *H pylori* status. Systemic inflammation was deemed absent if body temperature, leucocytes, C reactive protein (CRP), and erythrocyte sedimentation rate (ESR) were within normal ranges. Subgroups were defined according to *H pylori* status, IHD, and plasma fibrinogen in the presence or absence of systemic inflammation.

Table 1 Inflammation parameters and plasma fibrinogen before and after H pylori eradication

	Before eradication		*After eradication*		
	First contact	*Before treatment**	*1 month*	*3 months*	*6 months*
Leucocytes ($\times 10^9$/l)	7.14	6.81	6.70	6.23	6.89
CRP (g/l)	0.007	0.006	0.013†	0.007	0.006
ESR (mm 1st h)	11	12	20†	8	9
Fibrinogen (g/l)	4.13‡	3.43§	4.62†	3.21§	3.27§
(SD)	(0.43)	(0.89)	(0.20)	(0.32)	(0.63)

Values are means.
*3 to 12 months after first contact.
†Raised values because two patients had respiratory infections at that time.
‡$p < 0.01$ (paired *t* test) compared with first contact or 6 months.
§$p < 0.01$ (paired *t* test) mean of first contact and before treatment compared with the mean of 3 and 6 months after eradication.

Of 317 patients, 245 (77%) had IHD with a stenosis ⩾ 70% of at least one vessel, 127 (40%) had IHD and *H pylori* infection. Forty nine of these 127 (15% of all patients) also had raised fibrinogen (> 3.5 g/l). Only 20 of these 49 patients had normal systemic inflammation parameters (6% of all patients). A causal association between IHD and *H pylori* infection was suspected for these patients. This hypothesis was supported by a higher prevalence of raised fibrinogen in *H pylori* positive patients with IHD in the absence of systemic inflammation (35.1% *v* 17.5%; $p = 0.05$, one sided χ^2 test; relative risk (RR) 1.7; odds ratio (OR) 2.0; 95% confidence interval (CI) 0.9 to −4.6). Comparing only patients with increased fibrinogen without systemic inflammation, the prevalence of IHD was higher in *H pylori* positive patients (95% *v* 63.6%; $p < 0.05$, one sided χ^2 test; RR 1.3; OR 7.3; 95% CI 0.7 to −73). By performing multiple regression analysis, serologically determined positive *H pylori* status was significantly ($p < 0.001$) associated with raised plasma fibrinogen after adjusting for age, history of peptic ulcer, CRP, ESR, and leucocyte count. Bivariable analysis of these parameters influenced fibrinogen levels (but not IHD). Because of their dyspeptic symptoms, 12 of the above mentioned 20 patients agreed to be tested for active *H pylori* infection by ^{13}C urea breath test and 11 of 12 were positive and included in an *H pylori* eradication trial described elsewhere,[6] 10 of them becoming negative. After obtaining written informed consent we had the opportunity to follow up these 10 patients for 6 months (table 1).

In conclusion, *H pylori* infection may be regarded as a risk factor for IHD in a very small proportion of patients (6%, borderline significance). Our results may explain why even large epidemiological studies do not show a significant association between *H pylori* infection and IHD.[1] Raised plasma fibrinogen could be a link for the development of IHD in this predefined subgroup. Treatment (*H pylori* eradication) leads to a decrease of plasma fibrinogen in single cases with a known low risk of *H pylori* reinfection. However, in the individual patient there is striking evidence to assess fibrinogen repeatedly: spontaneous fluctuations (as seen in two of 10 patients) can possibly reflect the stability or instability of IHD[5] or interfering concomitant diseases. Before making a decision whether to treat hyperfibrinogenaemia with *H pylori* eradication, the absence of all other signs of systemic inflammation is essential.

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